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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,405	08/21/2000	Michael P. Neeper	20413Y	8029

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,405	NEEPER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,10,11,15,17-23 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10,17,19-23 and 30* is/are rejected.

7)☒ Claim(s) *7,11,15 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to amendment filed December 8, 2003. Claims 24-26 and 28 have been cancelled. The previous rejection in the Office action of Paper No. 16 is withdrawn in view of the cancellation of the rejected claims. Claims 1-4, 6, 7, 10, 11, 15, 17-23, and 30 are pending in the application.

Upon further review, the following new grounds of objection and rejections are necessitated. Prosecution is hereby REOPENED.

Claim Objections

Claims 1-4, 6, 7, 10, 17, 20, 23 are objected to because a comma should be inserted before the "wherein" phrases.

Claim 4 is objected to because the word "which" should be replaced with "wherein the polynucleotide" so that the claim is more clear.

Claims 7, 11, 15, and 18 are objected to because it is redundant to use both figure number and sequence identification number to identify the same sequence.

Claim 22 is objected to because the word "wherein" should be inserted before "the expression cassette" in line 2.

Claim 30 is objected to because the phrase "comprising" in line 2 should be replaced with "wherein the method comprises", and a phrase "whereby making a codon-optimized HPV 16 protein" should be added to the end of the claim to make the claim more clear.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said polynucleotide sequence" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "which" in line 2. It is unclear what "which" stands for, thus, the metes and bounds of the claim are uncertain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

The prior rejection of claims 24-26 and 28 under 35 U.S.C. 112, first paragraph, now applies to claim 30 because the specification, while being enabling for inducing an immune response to HPV16 infection in a subject using a polynucleotide encoding a codon-optimized HPV16 protein by intramuscular injection of the polynucleotide, does not reasonably provide enablement for inducing a protective immune response to HPV infection in a subject using a polynucleotide encoding a codon-optimized HPV16 protein

by *any* route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 30 is drawn to a method of making a HPV 16 protein in a human host cell using a polynucleotide comprising a codon-optimized synthetic polynucleotide encoding HPV 16. Given the broadest reasonable interpretation, the claim reads on making the protein in a human subject for purpose of genetic vaccination. As such, the issues relating to claims 24-26, and 28 are applicable to claim 30.

Amending the claim by inserting "an isolated" before the "human host cell" would obviate this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 10, 17, 21, 22, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Zolotukhin et al* (5,874,304), *Frazer et al* (6,489,141) or *WO 99/02694*, in view of *Ludmerer et al* (5,952,216), and *Apt et al* (6,399,383).

Zolotukhin et al teach using humanized versions of green fluorescent protein genes adapted for high level expression in mammalilan cells, especially human cells (e.g. abstract), and such are prepared by incorporating codons preferred for use in

human genes into the DNA sequence. They teach expression constructs comprising the humanized codon, and methods of using such for efficiently making GFP proteins in human cells (column 2, lines 11-22). *Zolotukhin et al* go on to teach that recombinant adenoviral vectors could be used to contain the humanized synthetic sequence (column 6, line 13). *Zolotukhin et al* do not particularly teach papillomavirus proteins.

Frazer et al or *WO 99/02694* teach a method of constructing a synthetic polynucleotide from which a protein is selectively expressible in a desired cell of a mammal, wherein at least one existing codon is replaced with a synonymous codon to produce a synthetic polynucleotide having altered translational kinetics, wherein the synonymous codon is selected such that it has a higher transnational efficiency in the target cell or tissue (e.g. abstract, column 2, lines 26-30, and column 10, § 2). They teach that papillomaviral late proteins such as L1 protein is very difficult to produce at a sufficient level (§ Background), and they use humanized codon expressing PV L1 and L2 to increase the efficiency in various cells (example 2 and 8). *Frazer et al* or *WO 99/02694* do not particularly teach making HPV 16 proteins.

Ludmerer et al teach that HPV-16 is responsible for epithelial dysplasia and are associated with many types of invasive carcinomas (column 1, lines 36-46), and the desirability to produce HPV-16 specific proteins including E1-E7, L1, and L2 for research and diagnosis. *Apt et al* teach that HPV 16 is highly oncogenic, and using various HPV proteins for developing vaccines.

Apparently, it is well known in the art that protein expression efficiencies vary between different cells or tissues and among mammalian cells and cells of other

species, and the differences could be exploited with codon composition of a gene to regulate and direct expression of a protein in a particular cell or cell type as taught by *Frazer et al,* or *WO 99/02694,* it is also well known in the art that one can use human preferred codons to enhance expression efficiency in human cells as taught by *Zolotukhin et al*; it is also well known in the art that there is a practical need for producing various HPV-16 proteins at significant levels as taught by *Ludmerer et al and Apt et al.* Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods taught by *Zolotukhin et al, Frazer et al* or *WO 99/02694* for efficiently producing HPV-16 proteins with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the improved efficiency of protein production. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 19, 20, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Zolotukhin et al* (5,874,304), *Frazer et al* (6,489,141) or *WO 99/02694*, in view of *Ludmerer et al* (5,952,216), and *Apt et al* (6,399,383) as applied to claims 1-4, 6, 10, 17, 21, 22, and 30 above, and further in view of *Ertl et al* ((US 6,019,978), and *Donnelly et al* (J Infect Diseases 1996;713:314-20).

The combined teachings of *Zolotukhin et al, Frazer et al or WO 99/02694, Ludmerer et al,* and *Apt et al* teach using adenoviral vector as the carrier for expressing

the synthetic polynucleotide, but fail to specify the features of the adenoviral vector or a V1Jns plasmid.

Ertl et al teach an adenoviral vector comprising complete or partial deletions in E1 and E3 region (abstract), the vector comprising a portion of a plasmid and a portion of adenovirus genome (figures, paragraph bridging columns 7 & 8) and a CMV promoter operably linked to polynucleotide coding region, wherein the encoded sequences in the E1 deletion site could be HPV L1, E6, and E7 (claims 2-4), wherein the vector could be used to induce a protective immune response against HPV (claims 1-6) via single or multiple dosing regimen (Example 3, for example).

Donnelly et al teach a polynucleotide comprising a sequence encoding a cottontail rabbit papillomavirus HPV11 L1 and L2 protein in an expression vector V1J derivative V1Jns (M & M section).

Evidently, it is known in the art that various vectors available in the art could be used for expressing a heterologous gene, especially HPV proteins. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combined the methods taught by *Zolotukhin et al, Frazer et al or WO 99/02694, Ludmerer et al,* and *Apt et al* using the vector of choice as taught by *Ertl et al and Donnelly et al* for efficiently producing HPV-16 proteins with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because given the numerous vectors known in the art, these limitations fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

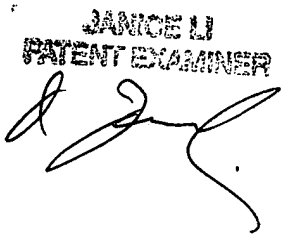
No claim is allowed. Claims 7, 11, 15, and 18 are free of cited prior art of record. However, they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
January 26, 2004